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Method for the preparation of 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepines.

A method for preparing certain 5,11-dihydro-6H-dipyrido(3,2-b:2',3'-e)[1,4]diazepines which comprises the following steps:

1. converting a 2,6-dichloro-3-pyridinecarboxamide to a 2,6-dichloro-3-aminopyridine by Hofmann Rearrangement;
2. reacting the 2,6-dichloro-3-aminopyridine with a 2-chloronicotonic acid to produce a 2,6-dichloro-3-(2'-chloro-3'-nicotiny)carboxamidopyridine;
3. reacting the 2,6-dichloro-3-(2'-chloro-3'-nicotiny) carboxamidopyridine with an amine to produce a 2,6-dichloro-3-(2'-amino-3'-nicotiny)carboxamidopyridine; and
4. hydrogenating the 2,6-dichloro-3-(2'-amino-3'-nicotiny)carboxamidopyridine to produce the 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepine.

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FIELD OF THE INVENTION

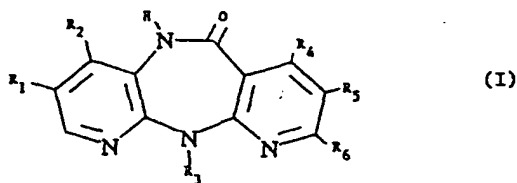
This invention relates to a novel method for preparing certain 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepines.

BACKGROUND OF THE INVENTION

Copending Philippine Patent Application No. 42529 describe novel 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepines useful in the prevention and treatment of HIV infection and methods for preparing these compounds.

SUMMARY OF THE INVENTION

Pyridobenzodiazepine compounds prepared by the novel process of this invention and from the novel intermediates described herein have the formula:



wherein R₁ is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, trihalomethyl, hydroxyalkyl of 1 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkanoylamino of 1 to 4 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, carboxyalkyl of 2 to 4 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, azido or halogen;

R₂ is hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that if R₁ is other than hydrogen or alkyl of 1 to 3 carbon atoms, then R₂ is hydrogen;

R₃ is alkyl or fluoroalkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkEnyl or alkynyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxyalkyl of 2 to 5 carbon atoms, preferably 2 to 4 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxy or halogen) or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms;

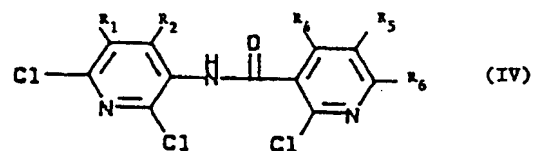
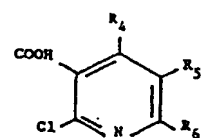
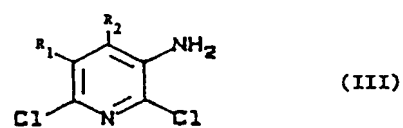
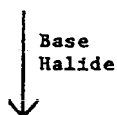
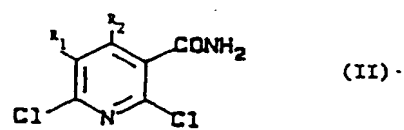
one of R₄, R₅, and R₆ is alkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, trihalomethyl, hydroxyalkyl of 1 to 4 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkyloxyalkyl wherein the alkyl moieties each contain 1 to 2 carbon atoms, hydroxyl, alkyloxy or alkylthio of 1 to 4 carbon atoms, hydroxyalkyloxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4 carbon atoms, alkanoyl of 2 to 6 carbon atoms, alkoxycarbonyl wherein the alkyl moiety contains 1 to 3 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, halogen, cyano, nitro, azido or carboxyl, with the other two substituents being hydrogen;

or, two of R₄, R₅ and R₆ are independently alkyl of 1 to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, or halogen, with the remaining substituent being hydrogen; or R₄, R₅ and R₆ are each hydrogen.

Preferably, R₁ and R₂ are hydrogen or alkyl of 1 to 3 carbon atoms, and R₃ is alkyl of 1 to 4 carbon atoms or cycloalkyl of 3 to 6 atoms.

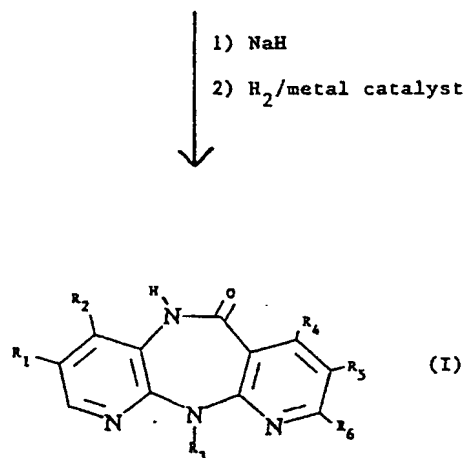
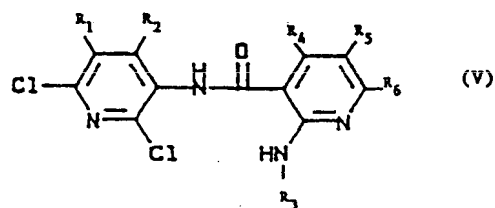
More preferably, R₁ and R₂ are hydrogen or alkyl of 1 to 3 carbon atoms; R₃ is cycloalkyl of 3 to 6 carbon atoms; and R₄, R₅, and R₆ are each hydrogen.

The process of this invention for the preparation of the compound of formula I is outlined below:



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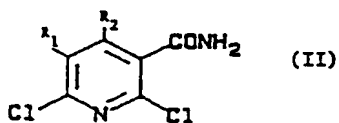
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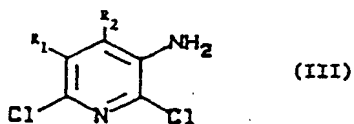
DETAILED DESCRIPTION OF THE INVENTION

40 The novel process of this invention for preparing the pyridobenzodiazepine of formula I comprises the following steps:

Step 1, reacting a compound having the formula

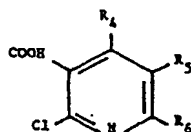


50 wherein R₁ and R₂ are as defined above, in an aqueous solution, with a base, such as NaOH, and a halide, such as bromine, chlorine or NaOBr, at temperature ranging from about 0° C to about 100° C, to produce a compound having the formula

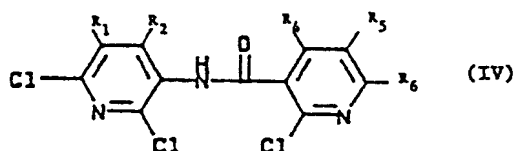


R_1 and R_2 have their starting values;

Step 2, reacting the compound produced in Step 1 with a compound of the formula

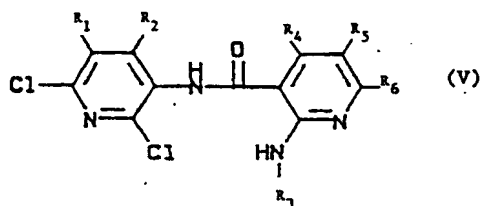


10 wherein R_4 , R_5 and R_6 are as defined above, in an anhydrous organic solvent, such as pyridine, between about 20 °C to about 80 °C (preferably about 70 °C), to produce a compound having the formula



20 wherein R_1 , R_2 , R_4 , R_5 and R_6 are the same as in the starting reactants;

Step 3, reacting the compound produced in Step 2 with R_3NH_2 , wherein R_3 is as defined above, in an inert organic solvent, such as diglyne or xylene, between about 20 °C to about 150 °C (preferably about 90 ° to about 110 °C), to produce a compound of the formula



35 wherein R_1 - R_6 are the same as in the starting reactants; and

Step 4, heating the compound produced in Step 3 in an inert organic solvent, such as pyridine, DMF or diglyne, comprising sodium hydride, between about 60 °C to about 150 °C; then hydrogenating the resultant solution in the presence of a metal catalyst, such as palladium, between about 20 °C to about 100 °C, to produce a mixture containing the compound of formula I; and then isolating the compound of formula I from the mixture.

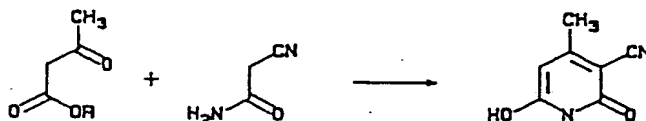
Preparation A below illustrates the preparation of the 2,6-dichloro-3-pyridinecarboxamide (compound of formula II) used to prepare the pyridobenzodiazepinone of Example I.

The compound may be isolated as such and, if desired, converted into a salt, e.g. an acid addition salt, or isolated from the mixture as a salt; known methods can be used for forming the salts.

The following Examples illustrate the preparation of various pyridobenzodiazepinones of formula I.

PREPARATION A

1) PREPARATION OF 3-CYANO-2,6-DIHYDRO-4-METHYLPYRIDINE



R = Ethyl

A mixture of 336g (4 moles) of cyanoacetamide, 507ml (520g, 4 moles) of ethyl acetoacetate, and 850ml of methanol was warmed to attain solution and 275g (4.18 moles) of potassium hydroxide dissolved in 220ml of methanol was added during 2 hours with stirring. During the addition a white precipitate formed and more methanol was added to prevent caking. The mixture was heated to reflux, stirred for 8 hours, cooled and filtered. The white precipitate was washed with methanol. The mono potassium salt was dissolved in warm water, filtered, cooled, acidified with concentrated hydrochloric acid, filtered, washed with water, and dried at 90 °C to yield 535g (89%).

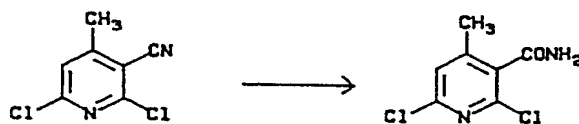
2) PREPARATION OF 3-CYANO-2,6-DICHLORO-4-METHYLPYRIDINE



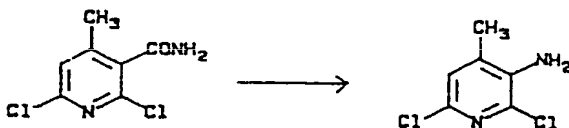
3-Cyano-2,6-dihydroxy-4-methylpyridine (50g, 0.33 mole) and phosphorous oxychloride (100ml, 1.07 mole) were placed in a glass lined stainless steel autoclave and heated to 140 °C for 8 hours. After cooling, the mixture was poured on ice and the crystalline product was filtered. The wet filter cake was dissolved in methylene chloride (100ml), dried over anhydrous $MgSO_4$, and concentrated to dryness. The material was crystallized from hot ethanol to yield 52.8g mp (102 ° - 106 °C) (85%).

The procedure was repeated substituting phenylphosphonic dichloride (b.p.258) (3 equiv.) for phosphorous oxychloride and heating the resultant mixture at 150 °C - 170 °C for 4 hours. A yield of 80% - 85% of 3-cyano-2,6-dichloro-4-methylpyridine.

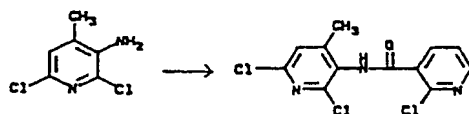
3. PREPARATION OF 2,6-DICHLORO-4-METHYL-3-PYRIDINECARBOXAMIDE



3-Cyano-2,6-dichloro-4-methylpyridine (80g, 0.42 mole) was dissolved in concentrated sulfuric acid (440ml). The mixture was heated at 150 °C - 170 °C with stirring for 30 minutes, cooled and poured on ice. The precipitate was filtered and washed with water. The wet filter cake was dissolved in methylene chloride, washed, neutralized with Na_2CO_3 , dried over Na_2SO_4 (anhydrous), and concentrated until a white precipitate separated. Petroleum ether was added, the crystals were filtered and dried at room temperature overnight to give 83g (94%) of 2,6-dichloro-4-methyl-3-pyridinecarboxamide.

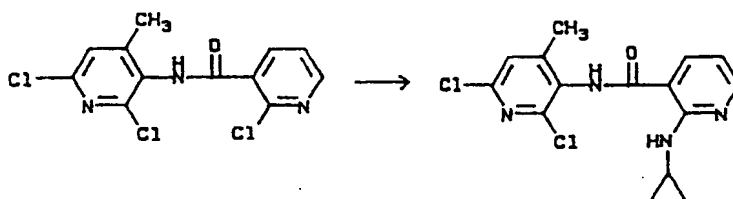
EXAMPLE IPREPARATION OF 11-CYCLOPROPYL-5,11-DIHYDRO-4-METHYL-6H-DIPYRIDO[3,2-b:2',3'-e][1,4]-DIAZEPIN-6-ONEA) PREPARATION OF 2,6-DICHLORO-4-METHYL-3-AMINOPYRIDINE

A solution of 89.2g (2.23 mole) of sodium hydroxide in 850ml of water was stirred and cooled to 0 °C in an ice/salt bath. 34.4 g (.668 mole) of bromine was added dropwise, maintaining the temperature at 0 °C. 120g (.585 mole) of 2,6-dichloro-4-methyl-3-pyridinecarboxamide was then added at once keeping the temperature at 0 °C-5 °C. The solution was slowly, over one-half hour, brought to room temperature and then heated at 70 °C-75 °C for one hour. The resulting suspension was cooled to room temperature, diluted further with 11 of water, and stirred overnight. The solid was filtered, back-washed with 11 of water, followed by 300 ml of petroleum ether and dried at 60 °C to give 89.4g (86.3%) (mp: 80 °C-83 °C) of tan crystalline 2,6-dichloro-4-methyl-3-aminopyridine.

B) PREPARATION OF 2,6-DICHLORO-3-(2'-CHLORO-3'-NICOTINYL) CARBOXAMIDO-4-METHYLPYRIDINE

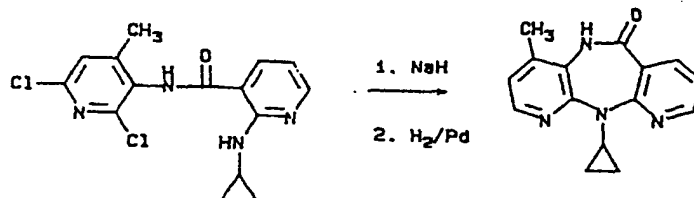
To a solution of 90.0 g (.508 mole) of 2,5-dichloro-4-methyl-3-aminopyridine in 225ml of cyclohexane, 220ml of pyridine, and 50ml of 1,4-dioxane was added in portions over 15 minutes a solution of 100.7g (.571 mole) of 2-chloronicotinic acid chloride in 200 ml of 1,4-dioxane. At the end of the addition, the reaction temperature reached 50 °C. The mixture was stirred at room temperature for 2 days. The wet filter cake was heated at mild reflux overnight in 11 of water containing 25ml of 1N NaOH solution. (The crude product contained 8%-10% of the di-adduct, which is readily hydrolyzed in dilute sodium hydroxide solution to the required product.) The product was collected by filtration and was washed with cold water. The pure product was dried at 60 °C under vacuum to yield 60g (37.3%) (mp:168 °C-171 °C) of 2,6-dichloro-3-(2'-chloro-3'-nicotinyl) carboxamido-4-methylpyridine.

2-chloronicotinic acid chloride was prepared by refluxing 90g (.571 mole) of 2-chloronicotinic acid in 315ml of thionylchloride for 2 hours. The excess thionylchloride was distilled off. The residue was diluted with 200ml of 1,4-dioxane and used as is.

C. PREPARATION OF 2,6-DICHLORO-3-(2'-CYCLOPROPYLAMINO-3'-NICOTINYL)CARBOXAMIDO-4-METHYLPYRIDINE

A mixture of 90g (.284 mole) of 2,6-dichloro-3-(2'-cyclopropylamino-3'-nicotiny)l carboxamide-4-methylpyridine and 79ml (1.14 mole, 4 eq.) of cyclopropylamine in 900ml of xylene was heated in a 21 stainless steel autoclave for 2 days at 90°C-110°C. After cooling, the xylene was concentrated to a paste and 11 of water was added. The resulting solid was filtered, back-washed with 11 of water, and 11 of petroleum ether.
 5 The product was dried at 80°C to give 80.5g (84.1%) (mp: 163°C-166°C) of 2,6-dichloro-3-(2'-cyclopropylamino-3'-nicotiny)l carboxamide-4-methylpyridine.

D. PREPARATION OF 11-CYCLOPROPYL-5,11-DIHYDRO-4-METHYL-6H-DIPYRIDO[3,2-b:2',3'-e][1,4]-DIAZEPIN-6-ONE



To a solution of 33g of 60% sodium hydride on mineral oil dispersion (.825 mole of sodium hydride) in 100ml of 2-methoxyethyl ether, heated to 120°C under nitrogen, was added dropwise over .5 hour 80g (.237 mole) of 2,6-dichloro-3-(2'-cyclopropylamino-3'-nicotiny)l carboxamide-4-methylpyridine in 400 ml of 2-methoxyethyl ether. The reaction mixture was stirred at 130°C-135°C for 1 hour longer, cooled to room temperature, and quenched by the careful addition of ethanol. The solution was then hydrogenated as is at 50 PSI with 8g of 10% palladium on carbon catalyst for 2 days. The catalyst was filtered and the ethanol was removed under reduced pressure. The methoxyethyl ether solution was poured into 31 of water and brought to pH7 with glacial acetic acid. The crystalline product was stirred overnight, collected and washed with pentane. The filter cake was dissolved in 500ml of hot pyridine and slow addition of 31 of water gave crystalline product. After aging overnight, the product was collected and suspended in 500 ml of isopropanol, heated to reflux, cooled and filtered. Final recrystallization from pyridine and water gave, after drying at 100°C, 45.8g (72.5%) (mp:253°C-254°C) of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one.

Example 2

11-Propyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

Prepared from 2,6-dichloro-3-pyridinecarboxamide, 2-chloro nicotinic acid and propylamine analogously to Example 1.
 mp 184-186°C

Example 3

11-Phenyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and phenylamine analogously to Example 1.
 mp 220-222°C

Example 4

11-Ethyl-5,11-dihydro-4-Methyl-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

Prepared from 2,6-dichloro-4-methyl-3-pyridine carboxamide, 2-chloro nicotinic acid and ethylamine analogously to Example 1.
 mp 212-214°C

Example 5

11-Ethyl-5,11-dihydro-9-methyl-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

- 5 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-6-methyl nicotinic acid and ethylamine analogously to Example 1.
mp 244-247 ° C

Example 6

10

11-Ethyl-3-methyl-5,11-dihydro-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

Prepared from 2,6-dichloro-5-methyl-3-pyridine carboxamide, 2-chloro nicotinic acid and ethylamine analogously to Example 1.

- 15 95% inhibition at 10µg/ml in the Reverse Transcription Assay

Example 7

11-Acetyl-5,11-dihydro-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

20

Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-nicotinic acid and methylcarboxamide analogously to Example 1.

>215 ° C (dec.)

- 25 Example 8

11-Ethyl-5,11-dihydro-3,4-dimethyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

- Prepared from 2,6-dichloro-4,5-dimethyl-3-pyridine carboxamide, 2-chloro-nicotinic acid and ethylamine analogously to Example 1.

30 mp 265-266 ° C

Example 9

35

11-Ethyl-5,11-dihydro-3-chloro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

2,5,6-trichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and ethylamine analogously to Example 1.
mp 217-218 ° C

- 40 Example 10

11-Ethyl-5,11-dihydro-7-methyl-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-4-methyl-nicotinic acid and ethylamine analogously to Example 1.

45 mp 193-194 ° C

Example 11

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11-Ethyl-5,11-dihydro-8,9-dimethyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-5,6-dimethyl-nicotinic acid and ethylamine analogously to Example 1.

mp 204-206 ° C

55

Example 12

11-Ethyl-5,11-dihydro-8-methyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

- 5 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-5-methyl-nicotinic acid and ethylamine analogously to Example 1.
mp 182-183 °C

Example 13

11-Ethyl-5,11-dihydro-4-ethyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

- 10 Prepared from 2,6-dichloro-4-ethyl-3-pyridine carboxamide, 2-chloro nicotinic acid and ethylamine analogously to Example 1.
15 mp 218-219 °C

Example 14

11-Ethyl-5,11-dihydro-8-bromo-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- 20 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-5-bromo-nicotinic acid and ethylamine analogously to Example 1.
mp 233.5-235.5 °C

25 Example 15

11-Isopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

- Prepared from 2,6-dichloro-4-methyl-3-pyridine carboxamide, 2-chloro nicotinic acid and isopropylamine
30 analogously to Example 1.
mp 188-189 °C

Example 16

35 11-Cyclobutyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

- Prepared from 2,6-dichloro-4-methyl-3-pyridine carboxamide, 2-chloro nicotinic acid and cyclobutylamine
analogously to Example 1.
mp 214-215 °C

40

Example 17

11-Cyclopropyl-5,11-dihydro-4-ethyl-6H-dipyrido[3,2-b:2'3'-e] [1,4]diazepin-6-one

- 45 Prepared from 2,6-dichloro-4-ethyl-3-pyridine carboxamide, 2-chloro nicotinic acid and cyclopropylamine
analogously to Example 1.
mp 228-230 °C

Example 18

50 11-Ethyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and ethylamine analogously to
Example 1.
55 mp 211-212 °C

Example 19

11-Isopropyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

- 5 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and isopropylamine analogously to Example 1.
mp 204-206 ° C

Example 20

10

11-Cyclopropyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4]diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and cyclopropylamine analogously to Example 1.
15 mp 240-250 ° C

Example 21

20

11-((R)-2-Butyl)-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and sec(R)butylamine analogously to Example 1.
mp 172-174 ° C

25 Example 22

11-((S)-2-Butyl)-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and sec(S)butylamine analogously to Example 1.
30 mp 173-175 ° C

Example 23

35

11-Cyclopentyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro nicotinic acid and cyclopentylamine analogously to Example 1.
mp 225-228 ° C

40

Example 24

11-Cyclopropyl-5,11-dihydro-4-methyl-7-hydroxy-6H-dipyrido[3, -b:2'3'-e][1,4] diazepin-6-one

- 45 Prepared from 2,6-dichloro-4-methyl-3-pyridine carboxamide, 2-chloro-4-hydroxy-nicotinic acid and cyclopropylamine analogously to Example 1.
mp 225-227 ° C

Example 25

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11-Cyclohexyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- Prepared from 2,6-dichloro-2-pyridine carboxamide, 2-chloro nicotinic acid and cyclohexylamine analogously to Example 1.
55 mp 199-201 ° C

Example 26

11-Ethyl-5,11-dihydro-7,9-dimethyl-8-chloro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- 5 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2,5-dichloro-4,6-dimethyl-nicotinic acid and ethylamine analogously to Example 1.
mp 160-162° C

Example 27

11-Ethyl-5,11-dihydro-7,9-dimethyl-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- 10 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloro-4,6-dimethyl-nicotinic acid and ethylamine analogously to Example 1.
15 mp 245-247° C

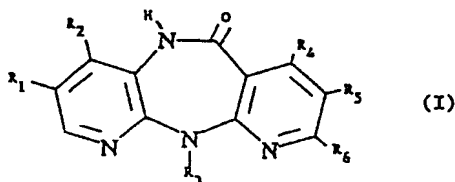
Example 28

11-Cyclobutyl-5,11-dihydro-6H-dipyrido[3,2-b:2'3'-e][1,4] diazepin-6-one

- 20 Prepared from 2,6-dichloro-3-pyridine carboxamide, 2-chloronicotinic acid and cyclobutylamine analogously to Example 1.
mp 241-243° C

25 **Claims**

1. A method for the preparation of a compound of the formula:



- 40 wherein R₁ is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, trihalomethyl, hydroxyalkyl of 1 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkanoylamino of 1 to 4 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, carboxyalkyl of 2 to 4 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, cyano, nitro, hydroxyl, carboxy, amino, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, azido or halogen;

- 45 R₂ is hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that if R₁ is other than hydrogen or alkyl of 1 to 3 carbon atoms, then R₂ is hydrogen;

- 50 R₃ is alkyl or fluoroalkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxylalkyl of 2 to 4 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxy or halogen), or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms;
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one of R₄, R₅ and R₆ is alkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, trihalomethyl, hydroxyalkyl of 1 to 4 carbon atoms, alkoxylalkyl or alkylthioalkyl of 2 to 4 carbon atoms,

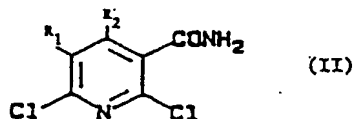
alkyloxycarbonylalkyl wherein the alkyl moieties each contain 1 to 2 carbon atoms, hydroxyl, alkyloxy or alkylthio of 1 to 4 carbon atoms, hydroxyalkyloxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4 carbon atoms, alkanyol of 2 to 6 carbon atoms, alkoxy carbonyl wherein the alkyl moiety contains 1 to 3 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, halogen, cyano, nitro, azido or carboxyl, with the other two substituents being hydrogen; or,

two of R_4 , R_5 and R_6 are independently alkyl of 1 to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, or halogen, with the remaining substituent being hydrogen; or

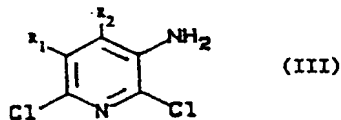
R_4 , R_5 and R_6 are each hydrogen,

which method comprises the following steps:

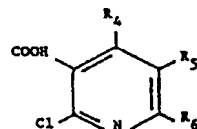
a) reacting a compound having the formula



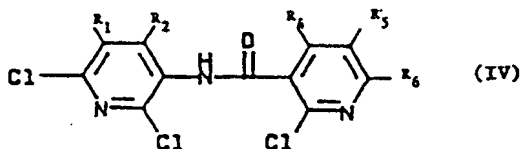
in an aqueous solution, with a base and a halide, at about 0°C to about 100°C, to produce a compound having the formula



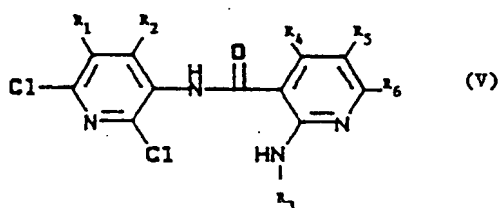
b) reacting the compound of formula III prepared in a), with a compound of the formula



wherein R_4 , R_5 , and R_6 are as defined above, in an anhydrous organic solvent, between about 20°C to about 80°C, to produce a compound having the formula



c) reacting the compound of formula IV prepared in b), with a compound of the formula R_3NH_2 , in an inert organic solvent at between about 20°C to about 150°C, to produce a compound of the formula



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d) heating the compound of formula V prepared in c), in an inert organic solvent comprising sodium hydride at between about 60 °C to about 150 °C; then hydrogenating the resultant solution in the presence of a metal catalyst, between about 20 °C to about 100 °C, to produce a mixture comprising the compound of formula I; and then isolating the compound of formula I from the mixture as such or as a salt thereof.

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2. A method as recited in claim 1 wherein R₁ and R₂ are each hydrogen or alkyl of 1 to 3 carbon atoms.
3. A method as recited in claim 2 wherein R₃ is alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 6 carbon atoms.
4. A method as recited in claim 3 wherein R₄, R₅, R₆ are each hydrogen.
5. A method as recited in claim 4 wherein R₃ is cycloalkyl of 3 to 6 carbon atoms.
6. A method as recited in claim 5 wherein R₁ is hydrogen.
7. A method according to claim 6, wherein the compound 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dihydro[3,2-b:2'3'-e][1,4]diazepin-6-one or a salt thereof is produced.

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European
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EUROPEAN SEARCH REPORT

Application Number

EP 91 11 7599

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,P	EP-A-0 410 148 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC. / DR. K. THOMAE GMBH) * page 3, line 34 - page 4, line 15 * * page 6, line 46 - page 7, line 32 * - - -	1	C 07 D 471/14 // (C 07 D 471/14 C 07 D C 07 D 243:00 C 07 D 221:00 C 07 D C 07 D 221:00)
A,P	EP-A-0 393 529 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC. / DR. K. THOMAE GMBH) * page 3, lines 2 - 29 * * page 6, lines 19 - 58 * - - -	1	
A	EP-A-0 066 774 (DR. K. THOMAE GMBH) * pages 1, 2; page 4 to page 5, line 11 * - - -	1	
A	DE-A-3 222 809 (DR. K. THOMAE GMBH) * claim 1 * - - -	1	
A	DE-A-2 424 811 (DR. K. THOMAE GMBH) * page 2, compound II * * page 4, last paragraph to page 6, line 2 * - - -	1	
A	DE-A-3 208 656 (CRC S.P.A.) * page 5, scheme 1 * - - - - -	1	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 471/00
Place of search		Date of completion of search	Examiner
Berlin		13 January 92	HASS C V F
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